

# Perspectives

## Anecdotal, Historical and Critical Commentaries on Genetics

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### Larry Sandler: Personal Recollections

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**F**OR many years Laurence Sandler (1929–1987) was my closest scientific colleague. He died suddenly and unexpectedly 12 years ago at the age of only 57. Larry was an original, and no tribute to him can be complete without anecdotes, some of which I will relate. During the previous three decades he had been among the leading *Drosophila* geneticists and perhaps the leading contributor of students; their impact on the field in the succeeding years continues to be immense.

Larry was born and raised in Brooklyn, and he often told stories of those days, many probably apocryphal. Despite being a city boy, from an early age he had an interest in agriculture, especially chickens. He claimed to have had a job during high school painting manure on cold-storage eggs so that they could be sold as farm fresh. He subsequently attended farm school in Farmingdale, Long Island; he described his failure in wall building—his wall fell over while being examined by the instructor—as motivating his decision to transfer to Cornell. He spoke fondly of his years at Cornell, where he discovered genetics and where he was able to attend courses in many disciplines taught by excellent professors; he became wedded to the academic life.

I first met Larry in 1952 while I was en route from Pasadena to my postdoctoral fellowship with Kenneth Cooper at Princeton University. I stopped in Columbia, Missouri, to visit Ed Novitski; he had been my *ex officio* mentor both when I was a master's degree student while Ed was a postdoctoral fellow at the University of Missouri and during my doctoral studies at Cal Tech, where Ed was a research fellow before he returned to the University of Missouri for a faculty position. Larry had recently arrived at Missouri from Cornell. He had hoped to study chicken genetics at Northern Illinois University in DeKalb; however, since no support was available in chicken labs, Adrian Srb advised him to accept an interim slot with Novitski. That summer I didn't see much of Larry because he was working in the corn fields for L. J.

Stadler. During the two decades prior to that time, the University of Missouri had become an outstanding center for research in plant genetics under the aegis of Stadler (see Roman 1988).

A year later I joined the Novitski laboratory for a second postdoctoral year. By that time Larry was Ed's pride and joy; he had absorbed *Drosophila* lore like a sponge, and all thoughts of chicken genetics had vanished. He and Gerry Braver had just submitted their paper on meiotic loss of unpaired chromosomes. At the same time Larry and Novitski were exploring the population consequences of nonrandom disjunction, which Novitski had described previously. They originated the seminal concept of meiotic drive as a force for changing allele frequencies in natural populations (Sandler and Novitski 1957). At the same time Larry was also investigating the origin of certain compound X chromosomes via reversed sister-chromatid exchange. During that year, he and I used adjacent microscopes and embarked on our first collaboration, on the meiotic behavior of small free-X duplications. It was after winter break of 1953–1954 that Larry returned from Brooklyn with his new bride, Iris; she immediately joined Novitski's lab as a graduate student. Years later, when introducing Larry to a seminar audience in Eugene, Ed enthused about the most promising graduate student that he had supervised and how it was his great pleasure to introduce her husband—the day's speaker.

In the summer of 1954, I moved to a position in the Biology Division of the Oak Ridge National Laboratory, but Larry and I continued our collaboration on the free duplications. Two years later, both Ed and Larry moved to Oak Ridge: Larry on a postdoctoral fellowship and Ed to head the *Drosophila* group, a position vacated a year earlier by Bill Baker, who had moved to the University of Chicago to occupy the slot freed by the retirement of Sewall Wright. At Oak Ridge, Larry and I completed our work on the duplications and sperm dysfunction. We found that some free-X duplications were transmitted at very low frequencies by males, but we could find no gametes from which they had been lost nor any

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appreciable zygote mortality; they had to have been lost sometime between meiosis and fertilization. We then embarked on a second project, that of applying Muller's doubler chromosome technique to the construction of the six possible configurations of compound X chromosomes, all marked with heterozygous markers for the eventual use in tetrad analysis. During that period we continued the practice, initiated in Novitski's lab in Missouri, of rigging the wall clock to run backward; it was confusing to anyone who did not work in the lab, but we had learned to read the mirror-image time without difficulty. Mary Lou Pardue, who was making cytological preparations in the lab at the time, says that today she sometimes gets confused about the direction that the minute hand is moving when she's timing staining procedures.

At the end of 1957, Novitski moved on to a faculty position at the University of Oregon, and I tried to convince Larry to remain in Oak Ridge. His heart, however, was set on returning to academia, and he had decided on Jim Crow's lab at the University of Wisconsin. Upon arrival he became fascinated by a chromosome that was preferentially recovered from males relative to its homologue, which had been isolated from a natural population in Madison by a first-year graduate student, Yuichiro Hiraizumi. It seemed to be a genuine case of meiotic drive acting in a natural population. This was *Segregation Distorter* (*SD*). Studies of *SD* led to the publication of eight substantial papers by Sandler and Hiraizumi over the next two years, and the phenomenon of segregation distortion was to occupy Larry off and on for the remainder of his career. The history of *SD* is summarized in a Perspectives article (Crow 1988), and a symposium on meiotic drive initiated by, and dedicated to the memory of, Larry appeared in the *American Naturalist* (Temin *et al.* 1991).

Larry had the habit of pacing back and forth while thinking; in Wisconsin, a long narrow office was planned to facilitate this predilection. At Madison, his interactions with James Crow and Sewall Wright introduced him to the disciplines of population genetics and evolution; this exposure prepared him to teach courses in those subjects in later years.

What turned out to be the first annual *Drosophila* Research Conference was held in Madison, Wisconsin in the fall of 1958. Larry, Bill Baker, Jim Crow, and I each presented our work for several hours. Ted Pittenger, a *Neurospora* geneticist from Marquette University, also discussed his work. Of course, other members of Crow's laboratory also attended and participated in the sessions; among them were Yuichiro Hiraizumi, Rayla Temin (then Greenberg), Elaine Mange (then Johansen), and Tom Gregg. R. A. Brink talked about his then current work with maize. What started out as an informal get-together of a handful of individuals to talk about flies has developed into an internationally attended yearly meeting that draws up to 1500 participants.

After two years as a postdoctoral fellow and two years as an Assistant Professor at the University of Wisconsin, where his course in cytogenetics was very popular, Larry was recruited by Herschel Roman to the Genetics Department at the University of Washington in 1961. The Sandler's two children, Jack and Dianna (Dee), were born in Madison.

Several of Larry's colleagues recount that when they invited him to join the Genetics Department at the University of Washington, they had the idea that he could provide students with some historical perspectives and instruction in classical genetics; the consensus at the time was that *Drosophila* genetics was passé and that he would probably not be active in supervising graduate students. They were in for a big surprise. Even though he never embraced molecular genetics, the students flocked to him, and he provided the field with a prestigious cadre of *Drosophila* researchers, including John Merriam, Leonard Robbins, Bruce Baker, Adelaide Carpenter, Jeff Hall, Barry Ganetzky, Scott Hawley, Ian Duncan, Joe O'Tousa, Paul Szauter, Larry Goldstein, Jim Mason, Kent Golic, and Bill Sullivan. Jon Tomkiel and Glenn Yasuda were both Ph.D. students in Larry's lab at the time of his death. They finished in other fly labs (Jon with Barbara Wakimoto and Glenn with Gerold Schubiger). Several investigators who spent sabbatical years with Larry are Arthur Mange, John Sved, Terry Lyttle, and Sergio Pimpinelli. Larry was preparing to spend a period in Sergio's lab in Bari, Italy, at the time of his death.

Larry was a dedicated teacher, both to large classes of undergraduates and to smaller groups of graduate students. To undergraduates he was both entertaining and popular; he was rigorous, but he never let his desire to cover the subject get in the way of a good story. He was also very effective one on one and in small groups. The accompanying photograph catches him in the act.

Larry was especially conscientious about teaching graduate students, and many of the graduate students in the department were greatly influenced by his teaching. He was fond of Socratic interactions with his students; he gathered them together weekly, and they would go over research papers in minute detail, examining experimental rationales, results, and conclusions in a question-and-answer format. He was pleased when the more senior graduate students instructed the new ones. He consciously weaned his students from his input over the course of their graduate careers, so that in their final year of thesis preparation they were essentially independent. Each student had an exclusive research project, and theses were invariably published as single-author articles, with Larry mentioned in the acknowledgments. The thrust of the experimental work in his laboratory was the investigation of the behavior of chromosomes during meiosis as elucidated through designed crosses and rigorous genetic analysis. Larry was unconcerned with the need to tackle popular topics; if



Laurence Sandler in 1984. Photo by Kent Golic.

the data posed an interesting question, that was incentive enough for him to accept the challenge. His approach was that of a scholar rather than that of someone whose main concern was catering to the current interests of the granting agencies; nevertheless, he never lacked for support.

In the summer of 1965, I drove with my family from Oak Ridge to Seattle to attempt with Larry the construction of a tandem compound ring X chromosome: two X chromosomes in the same sequence attached end-to-end and conjoined into a ring configuration. It was the last of six different heterozygously marked compound X chromosomes that remained for us to produce. Novitski had previously made and analyzed the progeny of all six, but without the advantage of heterozygous markers. We succeeded in making the tandem ring, and over the next four years he and I completed the tetrad analysis of three different tandem compound X chromosomes. During that summer Ed invited us down to Eugene to write a contribution to a volume on genetic techniques, being edited by Walter Burdette, about the use of compound-generating Bar-Stone duplications.

At the end of that summer Larry attended the Eleventh International Congress of Genetics in Bellagio, Italy. In the process he spent some time in Rome. He decided to take a stroll around the city; he wrote down the name of his hotel, Albergo, in case he got lost, so he could have a taxi return him. Fortunately he found the hotel by himself because, as he learned later, “albergo” simply means “hotel.” That visit to Rome convinced him of his desire to learn Italian and to return. He and Iris immediately began to study Italian, in which they became remarkably fluent. Years later, in preparation for a sojourn in Israel, Larry tackled Hebrew with the same ferocity as he had Italian. He insisted on speaking the local language when he was in those countries.

Larry and I decided to try to do a sabbatical year together in Rome. We met in his father’s apartment in Brooklyn and spent several days assembling a proposal to screen natural populations for recessive mutations affecting meiosis. It was an early attempt to apply the mutational approach, so successful in the dissection of metabolic pathways in microorganisms, to the study of a biological process in a higher eukaryote and to investigate what Charles Langley has termed the genetics of genetics. Luckily we were both funded, and we arrived *en famille* at the Institute of Genetics at the University of Rome, headed by Professor Giuseppe Montalente. We occupied adjacent apartments on the eighth floor of a building about four blocks from the institute. I had taken delivery of a new Volkswagen microbus in Paris, and we and the Slanders explored central Italy together on many weekends. We joined forces in Rome with Benedetto Nicoletti and a student, Gianni Trippa, and began to collect flies, first in the fruit market and later, at the time of the *vendemmia*, in the wineries on the outskirts of Rome.

Our first foray into the central fruit market provided the basis of one of Larry’s oft-told anecdotes. Because of his ineptitude with an insect net and his command of Italian, which was nearly perfect, it was my job to sweep for flies and his to explain my antics to the astonished onlookers. He explained that I was mentally unbalanced but harmless and that, in any case, he was there to make sure that I didn’t get out of hand.

Our genetic approach was to generate flies that carried marked X’s and 4’s and were homozygous for both chromosomes 2 and 3 derived from natural populations; the progeny of these flies were then scored for X chromosome recombination and X and 4 disjunction. We recovered half a dozen mutations that served as thesis material for Larry’s students in subsequent years. By confining our analysis to genomes in which both the second and third chromosomes were lethal free, we surely missed interesting meiotic mutants in lines in which one autosome carried a lethal. Among other mutants recovered were *SD-Roma*, the only nonrearranged *SD* chromosome available at the time, and abnormal oocytes, *abo*, a conditional maternal-effect lethal. A good



deal of Larry's effort in the ensuing two decades was dedicated to the characterization of *abo*.

Because our meiotic mutant hunt was so successful and enjoyable, Larry and I decided to embark on another joint venture, the generation of segmental aneuploids. The rationale was to bisect the large autosomes with a series of Y autosome translocations and then, by combining complementary elements of translocations with offset autosomal breakpoints, to generate interstitial duplications and deficiencies. At the beginning of the summer of 1970, the people in my laboratory (Rob Denell, George Miklos, Patricia Jacobs, and Bob Hardy) drove in four separate cars, one of which carried my cumbersome Ultraphot microscope, to Seattle to join forces with the members of Larry's lab (Bruce Baker, Adelaide Carpenter, Steve Miller, Dilys Parry, and Jeff Hall) to produce a large sample of Y autosome translocations. By the time we arrived in Seattle, the X irradiations had already been done, and the  $F_1$  crosses had been completed. All of us then began to score the individual  $F_2$  vials for pseudolinkage of the Y chromosome markers ( $y^+$  and  $B^s$ ) with the autosomes. We scored some 12,000  $F_2$  cultures and recovered over 450 Y autosome translocations. This part of the project was completed by the end of July.

We then began the determination of the autosomal breakpoints by polytene chromosome analysis. Of course, these determinations were not completed by the end of the summer and had to be continued into the fall quarter. Rob Denell, Pat Jacobs, and I finished the T(Y;2)'s back in La Jolla, while Bruce Baker and Adelaide Carpenter finished the T(Y;3)'s in Seattle. Toward the end of the fall quarter we were ready to make reciprocal crosses between attached XY males carrying one T(Y-A) to attached X females carrying an adjacent T(Y-A). We attempted to march down the chromosomes, insofar as available breakpoints would permit, at intervals of three- and six-lettered subdivisions of the polytene map. As all of these crosses began to emerge, the Sandler lab came to La Jolla for the winter break. We commandeered a student laboratory, and, together with additional La Jolla personnel (Richard Gethmann, Anita Hessler, Brian Davis, and Meredith Gould-Somero), we began to count the progenies of these nearly 7000 crosses. We were surprised to find that the majority of the three-letter deficiencies survived in heterozygotes, as did about half of the six-letter deficiencies. Furthermore, the frequent observation that the two three-letter deficiencies composing an inviable six-letter one survived led us to conclude that the deleterious results of heterozygous deficiencies were generally cumulative with size rather than owing to chance inclusion of a haplo-lethal locus. We took time off on Christmas Day 1970 to have a luau on the beach, but we had to take the food up to the picnic ground on the bluff above, because Larry refused to set foot on the beach; he wanted a picnic table and a folding chair.

In 1979 Iris Sandler received a Ph.D. in the history of science; she was so flustered at the graduation ceremony that she didn't realize that it was Larry who hooded her. During the eighties Larry and Iris explored the biological literature of the last century, trying to fathom why biologists of that time were unprepared to appreciate the work of Gregor Mendel. The Sandlers were continuing to enjoy delving into the history of genetics at the time that Larry died.

Of course, Larry performed the regular chores of reviewing grants and manuscripts and serving on study sections. In the early years he was uncomfortable with air travel, so to attend study sections he traveled from Seattle to Washington, DC, by train; he claimed that it gave him several days to review proposals. Larry served as associate editor of *Annual Review of Genetics* for 21 years, from its inception until the time of his death. He also served as associate editor of *Genetics* and sat on the Board of Directors of the Genetics Society of America; in the latter capacity he initiated the organization of the first international *Drosophila* genetics meeting in conjunction with the Sixteenth International Congress of Genetics, held in Toronto in 1983. In 1986, the fly meetings were being organized by different groups of geneticists: that year the meeting in Asilomar, California, was organized by the Seattle Fly Club. An innovation of that year was the introduction of abstracts. Larry personally guaranteed the occupancy of some 400 rooms; he realized that a blizzard or an airline strike could lead to his financial ruin. In response to this risk to the local organizer, he was influential in transferring the organization of the annual fly meeting and its associated risk to the Genetics Society of America.

He was obsessive in his habits. He took the same route to and from the university at the same time every weekday. He claimed that, were he to deviate from this route, he would get lost. He had his special chair for attending departmental seminars; woe unto the uninitiated who inadvertently usurped the chair. At his dissecting microscope, every item had its exact place on the desk top. His graduate students twitted him by painting outlines of the positions of his plate, etherizer, brush, and needle. The same sense of order could be seen on the tables in his living room at home: every knickknack had its defined position. If they were slightly disarranged, Larry would unconsciously return them to their original position upon entering the room. He had a mechanical calendar in his office; he turned it to the next day's date and sharpened two no. 2 pencils for the next day's use just before departing at exactly 5 p.m. He suffered, without comment, any attempt by his students to tease him by undoing either of these tasks. I include a quote from Kent Golc: "Larry was looking over my data one day and commented that I had only done one count (as you know, it was customary to count on days 14 and 18). I told him that it was not yet day 18. Larry mistakenly believed that I was only going to do one count because

I had not yet put a comma after the numbers that made up the day-14 counts. Larry said he always wrote the comma immediately because he knew that he would return for the next count."

When he added an activity to his schedule he was dogged in its pursuit. This certainly paid off in his mastery of Italian and Hebrew. The only endeavor in which he was unsuccessful was learning to play the guitar. I don't think he had the fingers for it; he could stopper a vial with his thumb. Although it seems out of character, Larry fancied himself an aficionado of boxing and bull fighting. I remember his excitement at the defeat of Sonny Liston by the then Cassius Clay during the tandem-ring summer.

He was less meticulous about his person. For many years he smoked too much, he ate too much (he was particularly fond of fatty foods), and he exercised too little. As a consequence, he became heavy and sedentary, and he had to give up pacing. At some point in the late seventies, Larry was having difficulty walking; he became concerned about his health, and he changed his lifestyle. He quit smoking, started dieting, and began swimming 50 laps per day in the university pool, starting at exactly 11:00 a.m. Ordinarily he did not go to the university on weekends, but in order to adhere to his swimming regimen he made an exception to that rule. He lost weight, grew a mustache, and upgraded his wardrobe. It was a remarkable transformation.

His colleagues in Seattle referred to Larry as a technophobe. I think that the most complicated piece of equipment that he ever operated by himself was a dissecting microscope. He never on his own initiative looked through a compound microscope; he shared with Novitski the view that nothing could be learned from cytology that could not be inferred from breeding experiments. He did have built and installed an electronic fly-counting apparatus designed for Ed Lewis. As far as I can make out, it was never used, either in Seattle or by Gary Karpen, who now has it in La Jolla. He even avoided using slides in lectures, although as a gag he would bring in slides to shuffle in his hands while lecturing. One more story was related to me by Dave Stadler: Larry

appeared one day wearing a gray lab coat, and Dave remarked that it looked just like the lab coat that his father (L. J. Stadler) used to wear. Larry replied that it was in fact that very same lab coat and that he had worn it on but two occasions, once in Missouri and this time in Seattle. Dave wondered what the occasions were; Larry confided that in both cases he had split the seat of his pants.

Larry was a voracious reader. He and Iris would visit the public library regularly and return home with a large stack of books to be read over the next week or so. He was a great raconteur and had a vast store of tales from his reading, many of which I heard repeatedly. They were also bibliophiles; the walls of their house are lined with completely filled bookshelves. There was no more room on the ground floor, and at the time of Larry's death they were well embarked on covering the upstairs walls. If the second floor has not collapsed under the weight, I imagine that Iris is still adding books. Larry read Italian and Hebrew as well as Yiddish and English. He made special efforts to obtain Italian books and subscribed to *Corriere della Sera*, an Italian newspaper.

His passing was deeply felt by the *Drosophila* community. Dedicated to his memory is the Sandler Memorial Lecture, which, in keeping with Larry's deep dedication to graduate teaching, is awarded annually for the best Ph.D. thesis on *Drosophila* of the previous academic year. The recipient delivers a plenary lecture on the opening night of the annual *Drosophila* Research Conference. The Genetics Department of the University of Washington also hosts an annual Sandler Lecture.

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